

PATIENT INFORMATION LEAFLET AND CONSENT FORM

COVID-19: Pandemic infection is either suspected or proven

STUDY TITLE: Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia (REMAP-CAP).

NAME OF PRINCIPAL INVESTIGATOR: Prof. Alistair Nichol

Consent was previously given on your behalf by your next of kin to take part in a research study and now you are being invited to continue or give your permission to participate in the study.

Now that you have recovered, we would like to tell you about the REMAP-CAP study and invite you to consider whether you wish to continue taking part in this research project.

You were enrolled because you have a condition called pneumonia which is an infection of the lungs caused by a new Coronavirus. The disease is called COVID-19.

Most patients with pneumonia due to COVID-19 who are being treated in an Intensive Care Unit will receive many different treatments, as many as 20 or 30 different treatments, that act together to treat both the infection and its effects on the body. For this research project:

- Several treatments may be tested, at the same time, in the same patient.
- We will tell you if you are not eligible for all options that are tested in the study.
- You can choose the parts of the study you participate in.
- Because COVID-19 is a new disease, doctors don't already know which treatments work best and the side effects of some treatment options.
- The study looks at its results as it goes and uses the results so that new patients in the study have a better chance of getting better treatments.
- The different treatment options are tested to tell which are the best. The study only tests options where it is not known which treatments are best.

About this Information Sheet and Consent Form

This Participant Information Sheet/Consent Form tells you about the research project. It explains the treatments involved and how it is determined which treatments you will receive. Knowing what is involved will help you decide if you want to continue to take part.

Please read this information carefully. Ask questions about anything that you do not understand or want to know more about. Before deciding whether or not you would like to continue to take part, you might want to talk about it with a relative, friend or the doctors who are treating you.

Participation in this research is voluntary. If you don't wish to continue to take part, you do not have to. If you choose not to continue to participate you will receive the best treatment the doctors can provide.

If you decide you want to continue to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

- Understand what you have read
- Agree to take part in the research project
- Agree to have the treatments that are described, so long as your doctor thinks they are appropriate
- Agree to the use of information about you and your health, as described.

You will be given a copy of this Participant Information and Consent Form to keep.

WHAT IS THE PURPOSE OF THIS STUDY?

The purpose of this research is to improve survival and recovery for patients with pneumonia.

We understand that being a patient with pneumonia can be very concerning. The doctors and the team associated with this research project are dedicated to giving you the best possible treatments.

Patients with pneumonia receive many different treatment options as part of standard care but doctors aren't always sure which of these treatments are best.

All of the medications used in this research project are already commercially available. Many of these have been suggested to be of benefit and have been used to treat patients with COVID-19 pneumonia. However, clinicians are unsure if they are truly effective against COVID-19 infection. This study is designed to resolve that uncertainty.

WHICH MEDICAL TREATMENTS ARE BEING INVESTIGATED?

In the REMAP-CAP study, several different treatments are being compared simultaneously
In this project, different aspects of treatment are being evaluated

1.COVID-19 – use of antiviral agents. There are some antiviral medicines that may work against COVID-19. Doctors don't know if any of them work or what side effects they may have. At this site, this project evaluates treatment with:

Lopinavir/ritonavir (also known as Kaletra)

OR

Hydroxychloroquine

OR

Hydroxychloroquine and Lopinavir/ritonavir (also known as Kaletra)

OR

No antiviral agent that is intended to be active against COVID-19



The doctors in this ICU have chosen these options because they don't know which option is best.

Treatment guidelines and recommendations from the World Health Organisation is that, for COVID-19, treatments with unknown benefit should only be administered in a clinical trial. The use of antivirals is not a usual treatment for COVID-19, so this evaluation is a "new treatment".

2.COVID-19 - use of immune modulation. There are some medicines that may work against COVID-19 by affecting the patient's immune system. Doctors don't know if any of them work or what side effects they may have. At this site, this project evaluates treatment with:

Interferon-beta 1a

OR

Anakinra

OR

No agent that is intended to modulate the immune response

The doctors in this ICU have chosen these options because they don't know which option is best. Treatment guidelines and recommendations from the World Health Organisation is that, for COVID-19, treatments with unknown benefit should only be administered in a clinical trial. The use of immune modulation is not a usual treatment for COVID-19, so this evaluation is a "new treatment".

3.Whether to use hydrocortisone. Hydrocortisone is an anti-inflammatory medication. Some doctors believe it helps reduce inflammation in the lungs and elsewhere in the body, and that this helps the body to recover. Other doctors disagree and don't use the medicine, and others use the medicine only when a patient is very unwell (is in "septic shock"). At this site, this project evaluates treatment with:

No corticosteroids

OR

A fixed duration of treatment with hydrocortisone

OR

Hydrocortisone given only when the patient is in "septic shock"

The doctors in this ICU don't know which treatment is best but believe all options are safe and reasonable. Therefore, the choice of whether to use hydrocortisone or not is comparing different types of "standard care".

4.Choice of antibiotic. All patients who doctors think have pneumonia are given antibiotics, but doctors give different antibiotics. At this site, this project evaluates the following antibiotics:

Ceftriaxone and a macrolide

Amoxicillin-clavulanate and a macrolide





The doctors in this ICU have selected to have these options available in the study because all of these options are known or believed to be safe and effective. If the participant is not in the study, it is very likely that the doctors would have treated them with one of these options. However, it is not known which option is best. The choice of antibiotic evaluates different types of “standard care”. The doctors in this ICU will be asked to consider whether the above antibiotics are appropriate for your individual medical presentation.

5.Duration of macrolide treatment. The medicine, **Clarithromycin** or **Azithromycin**, is a macrolide antibiotic that also has some anti-inflammatory actions. Most doctors give **Clarithromycin** or **Azithromycin** to most patients with pneumonia but stop after a few days. However, if it's stopped early the patient may not benefit from it's anti-inflammatory effect. In this research project, stopping **Clarithromycin** or **Azithromycin** after a few days will be compared with continuing it for up to 14 days. The longer course of **Clarithromycin** or **Azithromycin** is not a usual treatment, so this evaluation is a “new treatment”.

6.Use of influenza antiviral medications. When a patient has pneumonia caused by an influenza virus, some doctors will prescribe a drug called Oseltamivir, an antiviral medication. Some doctors do not routinely use Oseltamivir, and those who do may prescribe it for different lengths of time. At this site, this project evaluates treatment with:

Oseltamivir for five days

OR

Oseltamivir for ten days

The doctors in this ICU have selected these options because they do not know which of them is best, but believe that all of these options are safe and effective. Therefore, these options are different types of “standard care”. You will only receive these treatments if you have pneumonia that is believed or known to be caused by Influenza.

The following combinations of treatments will be used in this hospital:

- a) Ceftriaxone + 3-5 days Clarithromycin or **Azithromycin**
- b) Ceftriaxone + up to 14 days Clarithromycin or **Azithromycin**
- c) Amoxicillin-clavulanate + 3-5 days Clarithromycin or **Azithromycin**
- d) Amoxicillin-clavulanate + up to 14 days Clarithromycin or **Azithromycin**

Combined with

e) either hydrocortisone or no hydrocortisone or hydrocortisone given only when the patient is in “septic shock”

f) Oseltamivir for 5 days or 10 days

g) **Lopinavir/ritonavir (also known as Kaletra) or hydroxychloroquine or hydroxychloroquine and lopinavir/ritonavir or no antiviral agent that is intended to be active against COVID-19**

h) **Interferon-beta 1a or Anakinra or No agent that is intended to modulate the immune response**



The antibiotics and supportive treatments are being administered intravenously.
The antiviral is administered orally.

HOW WILL THE STUDY BE PERFORMED?

It concerns a randomised study. Randomisation is a process that can be compared to tossing a coin. Every participant has a 50% chance of receiving either of the two treatment options. In addition, this study uses an adaptive study design. This means that based on the study results, the chance of receiving one of the treatment options may change, in favour of the more promising treatment. You yourself will not notice any effect of this.

It is important for the treatment of your pneumonia that the antibiotics and supportive treatment selected are started as soon as possible. Therefore, these medicines were already assigned ("randomised") to you once you were admitted to the ICU. If you do not give your consent for participation in the study, your data will not be collected. The treatment started previously will in principle be continued and will be adjusted if the treating doctor considers this necessary.

If you give your consent for study participation after the discussion, your pneumonia will continue to be treated with the medication started previously, and this treatment will be adjusted if the treating doctor considers this necessary. In addition, data such as Temperature, Blood Pressure, Heart Rate and ventilator readings will be collected about you during the remainder of your stay in Intensive Care.

The data collected for the study is already being collected as part of your day- to-day medical care and no extra tests will be performed.

ARE THERE ANY RISKS OR BENEFITS FROM MY PARTICIPATION?

Medical treatments often cause side effects. The risks from side effects are similar if you choose not to be in the study. The doctor will know what treatment you are receiving at all times, and will be looking out for side effects. As these are all commonly used drugs, the doctors and nurses who will be caring for you while in the ICU are trained to recognise the risks associated with them. If side effects occur and the doctor thinks it's best to stop that treatment that is what will happen.

We cannot guarantee or promise that you will receive any benefits from this research.

WHAT ARE THE EXPECTED SIDE EFFECTS?

All medicines have side effects. As you are in intensive care and will be receiving various medicines, it is possible that you will experience side effects. The medication is also necessary, however, and can be life saving. It is not easy to determine which medicine is causing side effects. The medication in this study can cause side effects, from very minor to very serious. The doctor will weigh the side effects up against the advantages of medication. The doctor is convinced that this treatment is more important than the possible side effects that may occur. Whether or not the treatment in this study is still in your interest will be determined again every day. The medication will be adjusted if your doctor thinks this is necessary. The list of possible side effects can be found in annex 2.





Whether or not you will take part in the study is your decision. Participation is entirely voluntary. If you decide against participation, you will not need to do anything else. You will not need to sign anything. You will not need to give a reason for not taking part either. As a patient you will still receive the treatment you would otherwise receive. If you decide to participate, you can always change your mind and withdraw from the

study, even once the study has already started. Furthermore, the doctor may decide to discontinue participation in the study if they believe it is no longer in your best interest to participate. Moreover, inspection authorities have the right to interrupt or discontinue the study at any time.

FOLLOWING DISCHARGE FROM HOSPITAL

You will be contacted by a trained research co-ordinator by telephone at approximately 6 months after participation started in this research study to collect information on your recovery.

The trained research coordinator will collect information on your quality of life. It is expected this phone call will take about 10 minutes. In order for this phone call to take place, we will ask you to supply your contact phone numbers for this phone call.

CONFIDENTIALITY

Please find the details on confidentiality in Annex 1.

COMPENSATION

Your doctors are adequately insured by virtue of their participation in the Clinical Indemnity Scheme.

WHO IS ORGANISING AND FUNDING THIS RESEARCH?

This study is organised and funded by the European Commission FP7 program, and this study has been endorsed by the Irish Critical Care Trials Group.

HAS THIS STUDY BEEN REVIEWED BY AN ETHICS COMMITTEE?

The St. Vincent's Healthcare Group, Ethics and Medical Research Committee have reviewed and approved this study.

CONTACT DETAILS

If you need further information, please contact Professor Alistair Nichol Alistair.nichol@ucd.ie
Phone No: 01 7165826

Research Participants Rights

If you have any questions about your rights as a research participant, then you may contact the Hospitals Quality & Patient Safety Department 01 2214013



Annex 1:

CONFIDENTIALITY & DATA PROTECTION

Your identity will remain confidential. A study number will identify you (pseudo anonymised). Your name will not be published or disclosed to anyone. No identifying material will be used in any reports of this study. Records for the study will be kept in a secure filing cabinet in a secure office located at St Vincent's University Hospital. Research Coordinators and the Investigator listed on the front of this consent form will have access to your study data. Your health records, and any information obtained during the study are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities and authorised representatives from St Vincent's University Hospital or as required by the law. By the signing of the consent section, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

Would the information obtained in this study be kept confidential?

University Medical Center Utrecht is the Sponsor for this study (the institution who is responsible for oversight of the study). We will be using information from your medical records in order to undertake this study.

If you withdraw from the study, pseudonymised data recorded up to the point of withdrawal will be included in the study analysis unless you request otherwise.

PROCESSING OF YOUR PERSONAL DATA

St Vincent's University Hospital will process your personal data for the following purposes on the basis of your consent:

Personal data	Purpose of processing
1. Identification e.g. name, address, DOB (please note this and subsequent information will be anonymised/coded once leaving SVUH)	1. (a)Originally captured as part of medical care (b) used for purpose of carrying out research
2. Test results	2. Clinical care, safety measures, research outcomes
3. Clinical History (not identifiable)	3. PMH relevant to study outcomes
4. Questionnaires	4. PROMS required to measure response to treatment

Where does St. Vincent's University Hospital obtain my personal data from?

Most of the personal data we process is obtained from you directly but we also obtain personal data about you from your

- medical notes,
- lab test results,
- x-ray results,

SHARING OF PERSONAL DATA

Your personal data will in particular be shared with:

*NOTE: These parties will either be acting as Processors of your information as part of this research study e.g. CROs, non-SVUH employees supporting research process or Controllers in their own right.

Person/Company/institute	Requirement for sharing
Sponsor's monitor (UMC Utrecht)	Data quality control

Service Providers

We use third party service providers who provide services including financial services, occupational health and IT services. In providing the services, your personal data will, where applicable, be processed by the service provider on our behalf.

We will check any third party that we use to ensure that they can provide sufficient guarantees regarding the confidentiality and security of your personal data. We will have written contracts with them which provide assurances regarding the protections that they will give to your personal data and their compliance with our data security standards and international transfer restrictions.

Disclosures to Third Parties

In certain circumstances, we share and/or are obliged to share your personal data with third parties outside St. Vincent's Hospital, for the purposes described above and in accordance with Data Protection Legislation.

These third parties include but are not limited to:

- the Health Products Regulatory Authority;
- the Health Service Executive;
- the Joint Commission International;
- relevant industry bodies;
- external professional advisors; and
- others, where it is permitted by law, or where we have your consent.

To assist with rapid generation of knowledge in the COVID-19 pandemic, we will share de-identified research data and findings relevant to the novel coronavirus (COVID-19) outbreak with public health and research communities and the World Health Organisation (WHO).

TRANSFERS OUTSIDE THE EUROPEAN ECONOMIC AREA

Your personal information will be transferred, stored and processed in Australia which is outside the European Economic Area ("EEA"). For transfers of your personal data to third parties outside of the EEA, we take additional steps in line with Data Protection Legislation. We have put in place adequate safeguards with respect to the protection of your privacy, fundamental rights and freedoms, and the exercise of your rights, e.g. we establish an adequate level of data protection through EU Standard Contractual Clauses based on the EU commission's model clauses.

STORAGE OF PERSONAL DATA

We will keep your personal data for 15 years. This may mean that some Information is held for longer than other information.

STORAGE AND USE OF DATA FOR OTHER RESEARCH

Your data may also be useful for other scientific studies in the field of lung infections after this study has finished. Your data will be stored for 15 years in a data bank for this purpose. You can indicate on the informed consent form whether or not you accept this. If you do not agree to this, you can simply take part in the current study. This information will also be destroyed after 15 years.

YOUR RIGHT TO LODGE A COMPLAINT WITH A SUPERVISORY AUTHORITY

Without prejudice to any other administrative or judicial remedy you might have, you may have the right under data protection legislation in your country (where applicable) to lodge a complaint with the relevant data protection supervisory authority in your country (i.e. the Office of the Data Protection Commissioner in Ireland) if you consider that we have infringed applicable data protection legislation when processing your personal data. This means the country where you are habitually resident, where you work or where the alleged infringement took place.

For further information or if you have any questions or queries about this Participant Information and Consent Form, please contact:

By letter:

Orlaith McCarthy, Data Protection Officer, St Vincent's University Hospital
Elm Park, Dublin 4

By email:

dataprotection@st-vincents.ie

By telephone:

(01) 221 3591

Annex 2: List of Possible Side Effects:

Antibiotics: Diarrhea, dizziness, headache, stomach ache, tingling, nausea, vomiting, heartburn, a bad taste, swelling of mouth mucous membrane and tongue, worse sight, deafness, anorexia, itching, rash, joint pain, tiredness, phlebitis, general anaemia, arrhythmias, excessive sweating, shortness of breath, drowsiness, anxiety and confusion and nervousness;

Hydrocortisone can have the following side effects:

Water retention, nausea, increased risk of infection, high blood pressure, general malaise and hypersensitivity.

Oseltamivir can have the following side effects:

Headache, nausea, vomiting, stomach pain, diarrhoea, increased risk of infection, coughing, sore throat, general malaise and hypersensitivity.

Lopinavir/ritonavir may have the following side effects: Nausea, diarrhoea, vomiting, gastro-oesophageal reflux, pancreatitis and colitis. Hypersensitivity (including urticaria and angioedema). Skin infections or maculopapular rash, and night sweats. Anxiety, headache (including migraine), (peripheral) neuropathy, arthralgia, muscle spasms, asthenia. Hepatitis, increased levels of ALT, AST and γ -GT

Interferon beta-1a may have the following side effects: severe increase in aminotransferases, arthralgia, muscle ache/spasms, rigor, pruritus, rash, alopecia, diarrhoea, vomiting, nausea, depression, hypoesthesia.

Anakinra may have the following side effects: headache, infection, neutropenia, thrombocytopenia, raised blood cholesterol, injections site reaction, increase in hepatic enzyme action.

Hydroxychloroquine may have the following side effects: headaches, blurred vision, anorexia, cardiac disorders, gastrointestinal symptoms (vomiting diarrhoea, nausea, abdominal pain), rash, mood changes

Azithromycin may have the following effects: headache, diarrhoea, vomiting, abdominal pain, nausea, changes to blood counts (lymphocytes, monocytes, basophils, blood bicarbonate, eosinophils, neutrophils

Your doctor knows these side effects and others that may occur. In addition to the above-mentioned side effects, even more side effects occur, which are rare (affecting less than 1%).

CONSENT FORM

PLEASE TICK YOUR RESPONSE IN THE APPROPRIATE BOX

Date approached (dd/mm/yyyy) ____/____/____

Time (24 h, hh:mm): ____:____

Date decision (dd/mm/yyyy) ____/____/____

Time (24h, hh:mm): ____:____

Name participant: _____ Date of birth (dd/mm/yyyy): ____/____/____

- I have read and understood the Participant Information and Consent Form
YES ☐ NO ☐
- I have had the opportunity to ask questions and discuss the study YES ☐ NO ☐
- I have received satisfactory answers to all my questions YES ☐ NO ☐
- I have received enough information about this study
YES ☐ NO ☐
- I understand that I am free to withdraw from the study at any time without giving a reason and without this affecting my future medical care
YES ☐ NO ☐
- I am aware of the potential risks, benefits and alternatives of this research study.
YES ☐ NO ☐
- I consent to take part in this research study having been fully informed of the risks, benefits and alternatives. YES ☐ NO ☐
- I give informed consent to have my data processed as part of this research study.
YES ☐ NO ☐

STORAGE & FUTURE USE OF INFORMATION



I give permission for participation in (please indicate a choice for each line):

		Permission	No permission	Not applicable
1	Antibiotic domain	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2	Macrolide duration domain	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3	Steroid Domain	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4	Antiviral Domain	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5	Use of COVID-19 antiviral treatment	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6	Use of COVID-19 immune modulation therapy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7	Permission to use data from your medical record	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8	Permission to contact you to complete the follow-up questionnaires	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Participant's Signature: _____ Date: _____

Participant's Name in print: _____

Investigator's Signature: _____ Date: _____

Investigator's Name in print: _____



WITHDRAWAL FORM FOR PREVIOUSLY GIVEN CONSENT

Participation withdrawn by:

- ☐ patient
- ☐ Next-of-kin, name: _____
Relationship with patient _____

I hereby state that I withdraw (part of my) participation in the study.

This withdrawal is applicable to the following parts of the study (please indicate a choice on each line):

	Withdrawal	No change
Antibiotics domain	<input type="checkbox"/>	<input type="checkbox"/>
Macrolide domain	<input type="checkbox"/>	<input type="checkbox"/>
Steroid domain	<input type="checkbox"/>	<input type="checkbox"/>
Antiviral domain	<input type="checkbox"/>	<input type="checkbox"/>
Use of COVID-19 antiviral treatment	<input type="checkbox"/>	<input type="checkbox"/>
Use of COVID-19 immune modulation therapy	<input type="checkbox"/>	<input type="checkbox"/>
Permission to use data from your medical records	<input type="checkbox"/>	<input type="checkbox"/>
Permission to contact you to complete the follow-up questionnaires	<input type="checkbox"/>	<input type="checkbox"/>

Reason for withdrawal (not mandatory): _____

Name participant: _____

Date of birth participant (dd/mm/yyyy): ____/____/____

Date of withdrawal (dd/mm/yyyy): ____/____/____

Signature: